

## REMARKS

Claims 9, 16, and 96 have been cancelled without prejudice or disclaimer.

Claims 17, 46, 59-66, 77-80, 85, and 95 have been amended. Applicants have added no new claims. Claims 17, 46, 59-66, 77-80, 85, 87-92, 95, and 97 are currently under consideration.

Claim 17 has been amended to be an independent claim including certain limitations of prior claims 9 and 16. Claims 17 and 46 have also been amended to replace the word "or" with the word "and." Claim 17 has also been amended to replace the language "under stringent conditions" with the language "wherein the hybridization conditions comprise incubation in 5x SSC and 50% formamide at 42°C, and washing in 0.1x SSC and 0.1% sodium dodecyl sulfate at 60°C" in order to more clearly describe the conditions under which a sequence in the claimed invention would hybridize. Support for the amendment may be found in the specification, for example, at page 31, lines 7-14 and 31-33.

Claims 59-66, 77-80, 85, and 90 have been amended to remove the term "P45," and to replace the term "PEF" with the language "polymerase enhancing." Claim 64 has been amended to depend from claim 59. Claim 85 has been amended to insert the language "the amino acid sequence of," and to delete the reference to SEQ ID NO:72. Claim 17 has been amended to remove the language "a protein having a sequence comprising SEQ ID NO: 69 or 11, wherein the sequence comprising SEQ ID NO: 11 or 69 is within about 20 amino acids from the amino terminal end of the protein." Further, claims 17, 59-66, 77-80, 85, 90, and 95 have been amended to correct certain grammar.

These amendments add no new matter. The changes to the amended claims are shown in the marked up version of the claims in the attached Appendix.

Applicants also thank the Examiner for the acknowledgement that claims 46, 59-62, and 95 are free of the prior art.

#### Drawings

The Examiner states that the drawings are objected to for the reasons stated on the Notice of Draftsperson's Patent Drawing Review. Office Action, page 2, section 2. Substitute drawing are being submitted to the draftsperson concurrently with this Amendment.

#### Claim Objections

The Examiner objects to claims 9 and 17, suggesting that the group recited in the claim should include the term "and" rather than the term "or." Office Action, page 3, section 3. Without acquiescing to the Examiner's argument, claim 17 has been amended following the Examiner's suggestion. Claim 9 has been cancelled. The objection to claims 9 and 17 is moot.

The Examiner objects to claim 46 because of the recitation of the language "one of" in the phrase "one of SEQ ID NO: 19 or 71." *Id.*, section 4. Without acquiescing to the Examiner's argument, claim 46 has been amended to recite the language "at least one of SEQ ID NO: 19 and 71." The objection to claim 46 is moot.

The Examiner objects to claims 59-66, 77-80, 85, and 90 because of the recitation of the terms "P45" and "PEF." *Id.*, section 5. Without acquiescing to the Examiner's argument, claims 59-66, 77-80, 85, and 90 have been to remove the

abbreviations "P45" and "PEF." The objection to claims 59-66, 77-80, 85, and 90 is moot.

The Examiner objects to claim 64 because it depends from a non-elected claim. *Id.*, section 6. Without acquiescing to the Examiner's argument, claim 64 has been amended to depend from elected claim 59. The objection to claim 64 is moot.

The Examiner objects to claim 85 because of the recitation of the language "comprising one or more of SEQ ID NO: 72-73." *Id.*, section 7. Without acquiescing to the Examiner's argument, claim 85 has been amended to recite, in part, "comprising the amino acid sequence of SEQ ID NO: 73." The objection to claim 85 is moot.

#### Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejects claims 9, 16, 17, and 95 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. *Id.*, page 4, section 9.

#### Section 10

The Examiner rejects claim 9 for the recitation of the language "polymerase-enhancing protein complex of one or more wholly or partially synthetic proteins having the same amino acid sequence as the naturally-occurring protein" and the language "polymerase-enhancing protein complex comprising one or more of the naturally occurring or wholly or partially synthetic proteins." *Id.*, page 4, section 10. Without acquiescing to the rejection, and solely to expedite prosecution, claim 9 has been cancelled. Thus, the rejection of claim 9 is moot.

#### Section 11

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The Examiner rejects claims 17 and 96 as allegedly being indefinite for the recitation of the language "within about 20 amino acids from the amino terminal end of the protein." Office Action, pages 4-5, section 11.

Without acquiescing to the Examiner's argument, claim 17 has been amended to remove the language "a protein having a sequence comprising SEQ ID NO: 69 or 11, wherein the sequence comprising SEQ ID NO: 11 or 69 is within about 20 amino acids from the amino terminal end of the protein." Claim 96 has been cancelled without prejudice or disclaimer. Thus, this basis for the rejections of claims 17 and 96 is moot.

#### Section 12

The Examiner rejects claims 17, 95, and 96 for recitation of the language "sequence that hybridizes to the complement of the nucleotide sequence." *Id.*, page 5, section 12. Without acquiescing to the Examiner's rejection, the language of claims 17 and 95 have been amended to recite in part "a nucleic acid that hybridizes to the complement of the nucleic acid that ... ." Claim 96 has been cancelled without prejudice or disclaimer. Thus, this basis for the rejections of claims 17, 95, and 96 is moot.

#### Section 13

The Examiner rejects claim 17 because the language "stringent conditions" is allegedly unclear "absent a statement defining the conditions under which hybridization/wash reaction takes place." *Id.*, page 5, section 13. Without acquiescing to the rejection, the Applicant has followed the Examiner's suggestion, and claim 17 has been amended to recite certain specific hybridization conditions. The claims now recite the language "wherein the hybridization conditions comprise incubation in 5x SSC

and 50% formamide at 42°C, and washing in 0.1x SSC and 0.1% sodium dodecyl sulfate at 60°C.” Thus, this basis for the rejection of claim 17 is moot.

Applicants respectfully submit that claims 17 and 95 satisfy the requirements of 35 U.S.C. §112, second paragraph.

Applicants respectfully traverse the §112, second paragraph, rejections and request reconsideration and withdrawal of them.

#### Rejections Under 35 U.S.C. §112, First Paragraph

##### Written Description

The Examiner rejects claims 9, 16, 17, 63-66, 77-80, 87-92, and 97 under 35 U.S.C. § 112, first paragraph, as allegedly “containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors ... had possession of the claimed invention.” *Id.*, pages 5-9.

Without acquiescing to the rejection, and solely to expedite prosecution, claims 9 and 16 have been cancelled without prejudice or disclaimer. Thus, the rejections of claims 9 and 16 are moot.

With respect to claim 17, the Examiner asserts that “there is no disclosure of the function of a polypeptide comprising the peptides of SEQ ID NO:11 or 69, or a polypeptide encoded by a polynucleotide which hybridizes under any conditions to the polynucleotide of SEQ ID NO: 70.” *Id.*, page 6. Further the Examiner asserts that many “functionally unrelated peptides polypeptides are encompassed within the scope of these claims.” *Id.*, page 7.

Without acquiescing to the rejection, the language “a protein having a sequence comprising SEQ ID NO: 69 or 11, wherein the sequence comprising SEQ ID NO: 11 or

69 is within about 20 amino acids from the amino terminal end of the protein" has been removed from the claim. Thus, the Examiner's argument regarding this term is moot.

Further, claim 17 has been amended to recite "a nucleic acid that hybridizes to the complement of the nucleotide sequence of SEQ ID NO: 70, wherein the hybridization conditions comprise incubation in 5x SSC and 50% formamide at 42°C, and washing in 0.1x SSC and 0.1% sodium dodecyl sulfate at 60°C." The claim does not recite "a polynucleotide which hybridizes under any conditions to the polynucleotide of SEQ ID NO: 70." The Examiner's argument regarding this term is moot.

Thus, Applicants request reconsideration and withdrawal of the rejection of claim 17 under the written description requirement of 35 U.S.C. §112, first paragraph.

With respect to claim 63, the Examiner asserts that the "specification only discloses one species of the claimed genera which is insufficient to put one of ordinary skill in the art in possession of the claimed genera." *Id.*, pages 7 to 8, section 17.

Without acquiescing to the rejection, and solely to expedite prosecution, claim 63 has been amended to recite an "antibody that binds to a protein comprising the amino acid sequence of SEQ ID NO: 71, wherein the protein is part of the polymerase-enhancing complex of claim 61." Thus, this basis for the rejection of claim 63 under 35 U.S.C. §112, first paragraph, is moot.

With respect to claims 64-66 and 77-80, the Examiner asserts that "there is no disclosure of the structure or function of other proteins having a molecular weight of 45 (P45) or 50 KDa (P50) from *P. furiosus* or other organisms." Office Action, pages 8-9, section 18.

Without acquiescing to the rejection, and solely to expedite prosecution, claim 77 has been amended to recite a "protein comprising the amino acid sequence of SEQ ID NO:71." Claims 78-80 ultimately depend from claim 77. Claims 64-66 ultimately depend from claim 59. Claim 59 recites "a sequence encoding the amino acid sequence of SEQ ID NO: 71."

Thus, this basis for the rejection of claims 64-66 and 77-80 under 35 U.S.C. §112, first paragraph, is moot.

With respect to claims 87-92 and 97, the Examiner states that there is no disclosure of proteins from *Thermus thermophilis* that have dUTPase activity. *Id.*, page 9, section 19. Further, the Examiner states that there is no disclosure of the critical structural elements a homolog of the polypeptide of SEQ ID NO: 71 should have to display dUTPase activity. *Id.*, page 9, section 19.

Claim 87 recites in part a "protein extract comprising purified proteins from *Thermus thermophilis* that possess dUTPase activity." Claims 88-92 and 97 ultimately depend from claim 87.

The specification describes the use of a *Thermus thermophilis* dUTPase enzyme, for example, at page 18, lines 13-15, and at page 60, lines 5-12. Further, the specification discusses work that demonstrates dUTPase activity in *T. thermophilis* samples. See Specification at page 60, lines 5-12. In addition, the specification discloses regions of identity and regions of similarity of P45 to several dUTPases. See specification at page 42, line 2, to page 44, line 26.

Thus, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 87-92 and 97 under the written description requirement of 35 U.S.C. §112, first paragraph.

### Enablement

The Examiner rejects claims 9, 16, 17, 85, and 96 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. *Id.*, pages 9-12, section 20. Specifically, the Examiner states the specification does not provide enablement for a protein complex comprising a protein from *P. furiosus* comprising the peptides of SEQ ID NO: 69 or 11, or "any protein encoded by a polynucleotide which hybridizes under any condition to the polynucleotide of SEQ ID NO: 70."

Without acquiescing to the rejection, and solely to expedite prosecution, claims 9 and 16 have been cancelled, and claim 17 has been amended. Claim 17 reads in part "a protein encoded by a nucleic acid having the nucleotide sequence of SEQ ID NO: 70 or a nucleic acid that hybridizes to the complement of the nucleic acid having the nucleotide sequence of SEQ ID NO: 70, wherein the hybridization conditions comprise incubation in 5x SSC and 50% formamide at 42°C, and washing in 0.1x SSC and 0.1% sodium dodecyl sulfate at 60°C."

Claim 85 recites "a protein having polymerase-enhancing factor (PEF) activity comprising the amino acid sequence of SEQ ID NO: 73." SEQ ID NO: 73 is the uridine binding sequence of *P. furiosus* P45 (SEQ ID NO:71).

Claim 96 has been cancelled without prejudice or disclaimer.

One of skill in the art would know that a protein comprising the amino acid sequence of SEQ ID NO:73 would be a protein having a certain degree of similarity to



SEQ ID NO: 71, which has been demonstrated to possess polymerase enhancing activity throughout the specification.

Applicants respectfully assert that the Examiner is applying the enablement test incorrectly. As long as the specification discloses at least one method of making the invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement is satisfied. MPEP § 2164.01 (b). "Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. 112." *Id.*

It would not require one of skill in the art an undue amount of experimentation to determine whether any single given protein having a sequence comprising SEQ ID NO: 69 or 11, or a protein comprising SEQ ID NO: 73, possessed polymerase enhancing activity. A screening assay for polymerase enhancing activity is described in the specification in Example 1, pages 20-22.

In *In Re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988), the court reversed a finding of lack of enablement under §112, first paragraph. See MPEP §2164.06(b), under "Several Decisions Ruling That The Disclosure Was Enabling." The nature of the invention in that case involved the generation of monoclonal antibodies, and then screening the monoclonal hybridomas to determine which monoclonals possessed the desired characteristics. Although one of skill in the art could not predict the structure of all antibodies that would fit the claimed invention in that case, the court found that the specification was sufficient to allow one of skill in the art to determine which antibodies possessed the desired characteristics, and thus fell within the scope

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of the claims. Thus, the specification in *In Re Wands* was found to be enabling for monoclonal antibodies, the structure of which were not necessarily predictable.

Similarly, the specification in this case enables one of skill in the art to determine whether a given protein possesses polymerase enhancing activity. Such an assay does not represent undue experimentation. Under the enablement requirement, one need not be able to predict the exact structure of all proteins that possess polymerase enhancing activity. Rather, the specification only needs to enable one of skill in the art to determine whether a protein possesses polymerase enhancing activity.

The Examiner also states that the Applicant's argument, in the response filed July 29, 2002, with regard to the §112, first paragraph, enablement rejection of claims 9, 16, and 80, is deemed unpersuasive. Office Action, page 16-17, sections 26 and 27. Specifically, the Examiner states that, "[w]hile it is agreed that testing for polymerase enhancing activity can be performed with an assay, one would have to first isolate the polypeptides, analogs or protein extracts as encompassed by the claims to test for polymerase enhancing activity. Isolation of such polypeptides, analogs or protein extracts is not routine in the art for the reasons stated above." *Id.*, section 27.

Contrary to the Examiner's contention, the Examiner provides no particular reasons why isolation of polypeptides, analogs, or protein extracts is not routine in the art. Second, Applicants respectfully assert that isolation of polypeptides, analogs, and protein extracts was routine in the art at the time of filing. See, e.g., specification, page 20, lines 11-13 ("Methods of making extracts of these cells are known in the art ...."); page 47, lines 16-27; and generally Ausubel, F.M., et al (1989) *Current Protocols in Molecular Biology*, Greene Publishing Associates and Wiley-Interscience, New York,

NY; Sambrook, J. et al. (1989) Molecular Cloning: A Laboratory Manual, 2<sup>nd</sup> ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. At the time of filing, several commercial ventures produced chromatography columns, expression vectors, kits, and other reagents for the isolation of polypeptides and protein complexes. Applicants assert that the Examiner has failed to provide support for the statement that the isolation of polypeptides, analogs, or protein extracts is not routine in the art.

Further, claim 17 has been amended to recite in part "a nucleic acid that hybridizes to the complement of the nucleic acid having the nucleotide sequence of SEQ ID NO: 70, wherein the hybridization conditions comprise incubation in 5x SSC and 50% formamide at 42°C, and washing in 0.1x SSC and 0.1% sodium dodecyl sulfate at 60°C." Thus, the Examiner's argument regarding a "protein encoded by a polynucleotide which hybridizes under any condition to the polynucleotide of SEQ ID NO: 70" is moot.

For these reasons, the Examiner has not established that claims 17 and 95 fail to satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph. Thus, Applicants respectfully request reconsideration and withdrawal of that basis for the rejection.

The Examiner rejects claim 63 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. *Id.*, pages 12-13, section 21. Specifically, the Examiner asserts that "many other proteins of unknown function and structure which are part of the claimed protein complex have not been disclosed. An antibody which binds to any of the unknown proteins of the complex would be encompassed by the claim." *Id.*, page 13.

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Without acquiescing to the rejection, and solely to expedite prosecution, claim 63 has been amended to recite "an antibody that binds to a protein comprising the amino acid sequence of SEQ ID NO: 71, wherein the protein is part of the polymerase-enhancing complex of claim 61." Thus, the rejection of claim 63 under the enablement requirement of 35 U.S.C. §112, first paragraph, is moot.

The Examiner rejects claims 64-66 and 77-80 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. *Id.*, pages 13-14, section 22. Specifically, the Examiner asserts that the "specification, while being enabling for the P45 protein of SEQ ID NO: 71, does not reasonably provide enablement for any protein having a molecular weight of 45 KDa (P45) or analogs thereof." *Id.*, page 13.

Without acquiescing to the rejection, claim 64 has been amended to depend from claim 59, which recites "a protein produced from a cell containing a DNA construct comprising a sequence encoding the amino acid sequence of SEQ ID NO: 71." Claims 65 and 66 ultimately depend from claim 64. Claim 77 has also been amended to recite "a protein comprising the amino acid sequence of SEQ ID NO: 71." Claims 78-80 ultimately depend from claim 77. Thus, the rejection of claims 64-66 and 77-80 under the enablement requirement of 35 U.S.C. §112, first paragraph, is moot.

The Examiner rejects claims 87-92 and 97 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. *Id.*, pages 14-16, section 23. Specifically, the Examiner asserts that the "specification does not provide any guidance or examples of *T. thermophilis* dUTPases. No information has been provided on the critical structural elements required to identify a protein with dUTPase activity such as a catalytic domain, binding domain, etc. in *T. thermophilis* either." *Id.*, page 15.

Applicants respectfully assert that the specification discusses dUTPase activity in *T. thermophilis* samples. See specification at page 60, lines 5-12. Moreover, the specification discusses binding of an antibody raised against recombinant *P. furiosus* P45 protein (SEQ ID NO:71) to a band in *T. thermophilis* samples. The Examiner has failed to establish that it would require undue experimentation for one of skill in the art to determine if a protein bound in the band was responsible for the detected dUTPase activity. Such activity does not require knowing any of the critical structural elements of a dUTPase.

Thus, the Examiner has failed to establish that claims 87-92 and 97 are not enabled under 35 U.S.C. §112, first paragraph. Thus, Applicants respectfully traverse the §112, first paragraph, rejections of those claims and requests reconsideration and withdrawal of them.

#### Double Patenting

The Examiner rejects all considered claims as allegedly being unpatentable over claims of U.S. Patent No. 6,183,997, to Hogrefe ("Hogrefe") under the nonstatutory judicially created doctrine of obviousness-type double patenting. Office Action, page 18, sections 31 and 32.

Without acquiescing to the rejection, if the claims are otherwise found in condition for allowance, the Applicants will file a terminal disclaimer.

#### Conclusion

The application is in condition for allowance. Applicants request the timely allowance of the application. In the event the Examiner does not find the claims

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allowable, Applicants request that the Examiner contact the undersigned at (650) 849-6676 to set up an interview.

Please grant any extensions of time required to enter this Amendment and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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## APPENDIX

17. (Thrice Amended) A non-naturally occurring composition of matter comprising a protein complex possessing nucleic acid polymerase enhancing activity, the complex comprising a plurality of subunits wherein at least one subunit is a *P. furiosus* protein [A composition of matter according to claim 16, wherein said protein is] selected from [the group consisting of] at least one of:

[a protein having a sequence comprising SEQ ID NO: 69 or 11, wherein the sequence comprising SEQ ID NO: 11 or 69 is within about 20 amino acids from the amino terminal end of the protein;]

a protein encoded by a nucleic acid having the nucleotide sequence of SEQ ID NO: 70 or a nucleic acid [sequence] that hybridizes to the complement of the nucleic acid having the nucleotide sequence of SEQ ID NO: 70 [under stringent conditions], wherein the hybridization conditions comprise incubation in 5x SSC and 50% formamide at 42°C, and washing in 0.1x SSC and 0.1% sodium dodecyl sulfate at 60°C; [or] and

a protein having a sequence of amino acids comprising the amino acid sequence of SEQ ID NO:71.

46. (Amended) An antibody that binds to a protein having an amino acid sequence comprising at least one of SEQ ID NO: 19 [or] and 71.

59. (Thrice Amended) A [P45] protein produced from a cell containing a DNA construct comprising a sequence encoding the amino acid sequence of SEQ ID NO: 71 [PEF protein P45] operably linked to an expression vector, wherein the protein is in monomeric, dimeric, or multimeric form.

60. (Amended) [A P45 protein as claimed in] The protein of claim 59, wherein the cell is a bacterial cell.

61. (Amended) A polymerase-enhancing [PEF] complex comprising [a P45] the protein [as claimed in] of claim 59.

62. (Amended) An antibody that binds to [a P45] the protein [as claimed in] of claim 59.

63. (Amended) An antibody that binds to a protein comprising the amino acid sequence of SEQ ID NO: 71, wherein the protein is part of the polymerase-enhancing [a PEF] complex [as claimed in] of claim 61.

64. (Amended) The protein of claim 59 [A P45 protein produced from a cell containing a DNA construct as claimed in claim 58], wherein the [P45] protein is produced as a fusion protein.



65. (Amended) The [A P45] protein [as claimed in] of claim 64, wherein the fusion protein comprises a calmodulin binding peptide.

66. (Amended) The protein of [A P45 protein as claimed in] claim 65, wherein the expression vector is pCAL-n-EK.

77. (Amended) A non-naturally occurring composition of matter comprising a [P45] protein comprising the amino acid sequence of SEQ ID NO: 71.

78. (Amended) The [A] composition of matter of [as claimed in] claim 77, wherein the [P45] protein is in monomeric, dimeric, or multimeric form.

79. (Amended) The [A] composition of matter [as claimed in] of claim 77, wherein the [P45] protein is present in a protein complex.

80. (Amended) The [A] composition of matter [as claimed in] of claim 77, wherein the [P45] protein is an analog [P45] protein.

85. (Twice Amended) A protein having polymerase-enhancing factor (PEF) activity comprising [one or more of] the amino acid sequence of SEQ ID NO: [72-]73.

90. (Amended) A protein extract of claim 87, which comprises a protein that can be bound by an antibody specific for a recombinant Pfu [P45] protein comprising the amino acid sequence of SEQ ID NO: 71.

95. (Thrice Amended) A non-naturally occurring composition of matter comprising a polymerase-enhancing protein encoded by a nucleic acid [DNA sequence] that hybridizes to the complement of the nucleotide sequence of SEQ ID NO: 70, wherein the hybridization conditions comprise incubation in 5x SSC and 50% formamide at 42°C, and washing in 0.1x SSC and 0.1% sodium dodecyl sulfate at 60°C overnight.